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Music affects functional brain connectivity and is effective in the treatment of neurological disorders

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Abstract: In a million years, under the pressure of natural selection, hominins have acquired the abilities for vocal learning, music, and language. Music is a relevant human activity, highly effective in enhancing sociality, is a universal experience common to all known human cultures, although it varies in rhythmic and melodic complexity. It has been part of human life since the beginning of our history, or almost, and it strengthens the mother-baby relation even within the mother's womb. Music engages multiple cognitive functions, and promotes attention, concentration, imagination, creativity, elicits memories and emotions, and stimulates imagination, and harmony of movement. It changes the chemistry of the brain, by inducing the release of neurotransmitters and hormones (dopamine, serotonin, and oxytocin) and activates the reward and prosocial systems. In addition, music is also used to develop new therapies necessary to alleviate severe illness, especially neurological disorders, and brain injuries.

Keywords: dopamine; mental disorders; music; serotonin; synaptic plasticity.

Introduction

Modern studies consider music as one of the earliest human activities. Although musical ability is not unique to the human species, it appears to be related to the essential nature of our species and, conceivably, musical communication was fundamental to the life of our ancestors (Mithen et al. 2005).

Since ancient times music has been used to support essential collective moments in society and to alleviate sadness and pain.

What is music it is difficult to say, perhaps the definition would vary from individual to individual. One thing that we like to share is that music is sounds that arouse emotions. The emotional and evocative meanings of music probably differ from place to place and among listeners, constituting a singular *"soundscape"*, in accordance with socio-cultural, factors, experiences, and evoked memory. Music is a form of communication that does not need words to create rich and stimulating narratives, as transpires in the behavior of vocal and gestural games between babies and mothers or caregivers.

It is well documented that music affects many areas of the brain and musical training can significantly improve both motor and reasoning skills (Perrone-Capano et al. 2017). The inferior frontal gyrus is involved in generating speech and music in our mind independent of auditory perception. The Wernicke's area, located in the temporal lobe, is involved in understanding language, and interacts with the auditory network both during musical perception and musical imagery, through bilateral interactions, contradicting the generally accepted vision that music and language are processed separately in the two hemispheres (Zhang et al. 2017a). Listening to music engages not only the auditory cortex but also the emotion and reward-related mesolimbic circuits (Figure 1). Indeed, as described below, the music-associated benefits result from the activation of

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brain monoaminergic circuits, including serotonergic (5-HTergic) and dopaminergic (DAergic) pathways (Moraes et al. 2018). Listening to music and playing an instrument promote neural plasticity in specific brain areas: the new synapses can remodel the damaged neural connections, thus providing a noninvasive therapeutic tool to manipulate brain rewiring in acute and chronic neurological and psychiatric diseases.

Interestingly, music therapy can be positively applied to a broad range of disorders in addition to those affecting the nervous system. For instance, its beneficial effects were addressed in patients with head, neck, or breast cancer, where the music intervention significantly reduced anxiety and stress (Jasemi et al. 2016; Köhler et al. 2020; Li et al. 2020). Lastly, the beneficial effects of listening to music have been recently used to help handle the fear, anxiety, and pain related to the COVID-19 pandemic, also during the last phases of severe infection (Reidy and MacDonald 2021; Ribeiro et al. 2021).

Thus, in this review, we examine the neurobiology of listening to, and performing music, and we highlight the new insights about music as a nonpharmacological intervention to ameliorate the symptoms of aging, and in patients with several and severe illnesses, such as Alzheimer's (AD) and Parkinson's disease (PD), stroke, and autism spectrum disorder (ASD).

Music as a driver of brain plasticity

Neuroplasticity is the brain's ability to sculpt its architecture, adapting the neuronal connections and synaptic strength, throughout the life span in response to solicitations from the outside world and internal stimuli (Colucci-D'Amato et al. 2020; Speranza et al. 2021). Generally, the brain responds to external stimuli rewiring neuronal connections and, in specific areas, generating new neurons (Eisinger and Zhao 2018; Nakafuku and Águila 2020). The underlying mechanisms of neuroplasticity are extremely variable amongst individuals and throughout their lifetime (Voss et al. 2017). In the last years, neuroplasticity has become a central topic in studies focused on music and the brain. Music can be considered as an enriched environment able to solicit brain function (Jaschke et al. 2018): plastic adaptations can occur both through listening and performing music (Lappe et al. 2008). The latter is also correlated to other important factors like training age, training duration, personal preference, and emotional involvements (Reybrouck et al. 2018). For all these reasons, the musician's brain is an interesting model for the study of neuroplasticity, requiring the simultaneous integration of sensory and motor information combining auditory, visual perception, and pattern recognition skills (Reybrouck et al. 2018).

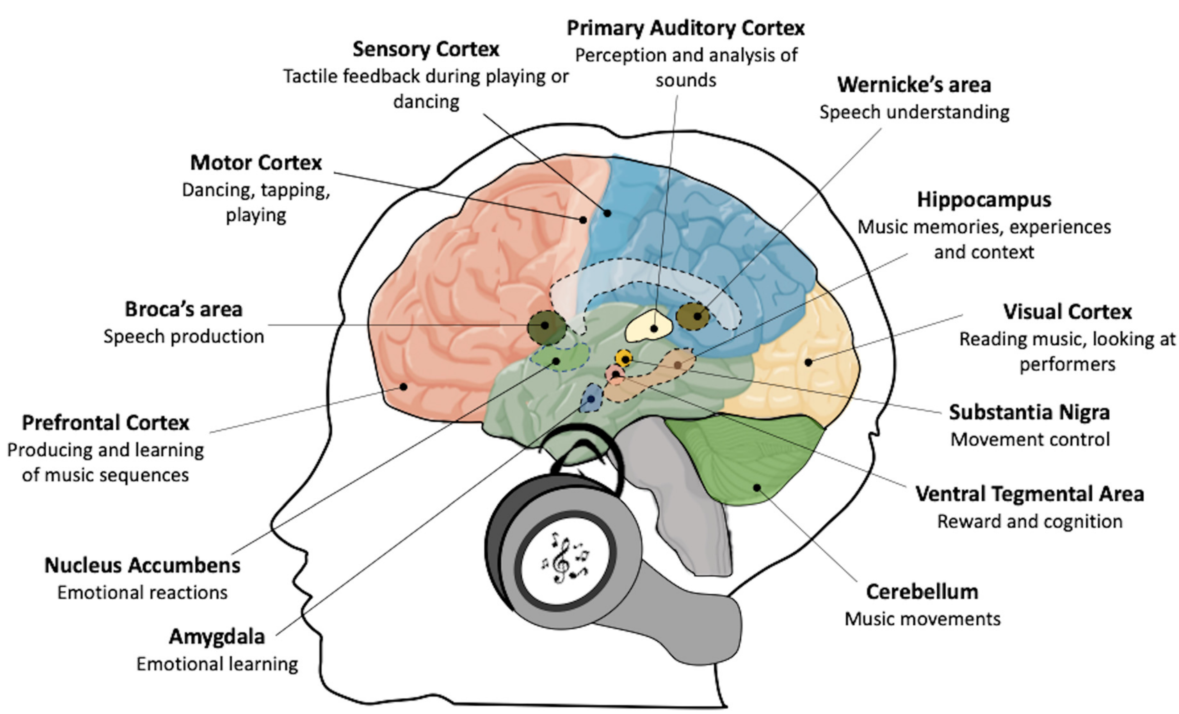

Figure 1: Schematic representation of different brain areas implicated in listening and playing music.

The development of innovative morphometric and neuroimaging tools allowed scientists to classify brain adaptations in macrostructural and microstructural changes. The former is related mostly to differences in the volume of cerebral target areas that are visualized with magnetic resonance imaging (MRI) (Keller and Roberts 2009). Instead, the microstructural adaptations occur at the level of the single neuron and synapse, affecting the brain connectivity, shaping the strength of existing synapses and the formation of new synapses (synaptogenesis), stimulating axonal sprouting, dendritic spine growth, and pruning (Altenmüller and Furuya 2017). The sum of the microstructural changes may support the differences that could be detected at a macrostructural level.

An example of macrostructural adaptation has been reported by Wan and Schlaug, showing that in a musician's brain, there is a larger anterior corpus callosum (Wan and Schlaug 2010), a bundle of millions of myelinated axons ($200–250 \times 10^6$) involved in the interhemispheric communication and required for the execution of complex bimanual motor sequences (Schlaug et al. 1995). This observed effect is also time-dependent: musicians who started at a young age (before 7 years) have a larger corpus callosum compared to musicians that started later (Wan and Schlaug 2010). In addition, the size of the primary motor cortex was mostly larger in the right hemisphere in musicians compared to nonmusicians, and like the corpus callosum, its volume was tightly linked to the time of the onset of the musical training (Amunts et al. 1997; Schlaug 2001).

Over time, other brain areas, that show structural differences between musician and nonmusician, have been identified: the Heschl gyrus or primary auditory cortex (Schneider et al. 2005), the planum temporal or secondary auditory cortex (Keenan et al. 2001), the Broca area (Sluming et al. 2002), and the inferior frontal gyrus (Gaser and Schlaug 2003). These areas in general appear to be more pronounced in musicians who started training early in life (Elbert et al. 1995; Schlaug et al. 1995) and who practiced with greater intensity (Gaser and Schlaug 2003; Hutchinson et al. 2003; Schneider et al. 2005).

Thus, music-related plastic changes are most prominent in musicians who started practice early in childhood, probably because neuroplasticity decreases with age. Moreover, it has been observed that the microstructural changes, induced by music training, such as developing and strengthening of neuronal connections, may enhance the ability of other brain areas, in addition to those involved in the music itself, a process defined as "skill transfer" (Bangerter and Heath 2004). For example, there is evidence highlighting the beneficial effects of music on cognitive development in children. Specifically, has been demonstrated that musical training could improve verbal abilities (Wan and Schlaug 2010), reading skills (Butzlaff 2000), and intellectual development (Schellenberg 2006) in children. Conversely, little evidence supports that musical training can improve mathematical performance (Forgeard et al. 2008).

Although convincing evidence showed the beneficial effects of music on overall cognitive ability in children, this point has been recently questioned, since contrasting observations have been reported. While Standley reported a modest but significant positive effect of music training on reading skills, Gordon, and colleagues proved a small impact of music training on phonological awareness but not on reading fluency (Gordon et al. 2015; Standley 2008).

Regarding the cognitive domains, Benz and colleagues showed a small – although significant – enhancing effect on various cognitive abilities, while a meta-analysis from Sala and Gobe failed to support the hypothesis of music skill transfers for cognitive abilities in young populations (Benz et al. 2016; Sala and Gobet 2017). Therefore, the role of music training in children's and young adolescents' cognitive abilities is still controversial.

Overall, neural dynamic changes triggered by music and experience can be modified throughout the whole life span. Increasing evidence supports the hypothesis that the mature brain is malleable in structural adaptations to respond to external stimuli. Therefore, the training-induced plasticity is not restricted to early development (childhood) but can also interest the mature brain (adulthood). An example is offered by the London taxi drivers showing larger hippocampal volume compared to non-taxi drivers or even bus drivers who drive in paths already constrained and always the same (Maguire et al. 2006).

The chemistry of music: dopamine and serotonin

Performing music requires multiple actions with very precise timings, such as the control of the range of tone, timbre, rhythm, and intonation and needs specific circuits that allow the production of sounds, singing, as well as language. These circuits enable the mind to perceive and analyze the sounds captured through the ear, locate, and memorize/remember them (Perrone-Capano et al. 2017). As said above, a large body of evidence demonstrates the tight relationship between music and language and highlights how the human brain uses shared networks to generate and control different functions. Language and music are ways of communication, which also occur through visual, hearing, chemicals (pheromones), or tactile signals. Music is able to change the chemistry in the brain, inducing the release of neurotransmitters, namely dopamine (DA) and serotonin (5-HT), that activate the reward system and hormone release (Salimpoor et al. 2011). As Chanda and Levitin argue, group music and singing increase the production of oxytocin in the brain (Chanda and Levitin 2013), produced by parvocellular neurons of the paraventricular nuclei of the hypothalamus and released into the circulation through the pituitary gland. Among other functions, oxytocin appears key to establishing and maintaining social bonds, both in adulthood and during formative periods of early life, thus facilitating music's social bonding effects (Hansen and Keller 2021). Thus, humans feel pleasure, which comes from a wide variety of stimuli and activities, such as food, sex, social contact, the so-called primary reinforcements (Speranza et al. 2021), or from aesthetic experiences, such as listening to music. Music induces a wide range of physiological effects on the human body, including, changes in respiration, heart rate, skin conductivity, blood pressure, skin temperature, muscle tension, and biochemical responses (Hodges 2010). All rewarding events, independently of their type, are processed by the ventral tegmental area (VTA), the ventral striatum, the anterior cingulate cortex, the orbitofrontal cortex, insula, and the amygdala (Haber 2011; Speranza et al. 2021). The ventral striatum is considered a key intersection of the reward circuitry, since it receives inputs from the limbic areas, such as VTA DAergic neurons, activated during rewarding experiences (e.g., during the use of addictive drugs), from the ventromedial prefrontal cortex, anterior cingulate cortex, and amygdala (Haber 2011). A remarkable series of studies has demonstrated the implication of the reward system in musical emotions. Neuroimaging studies have shown that music-associated-benefits are related to the activation of brain monoaminergic circuits, including DAergic and 5-HTergic pathways and their interplay with opioid pathways. Endogenous opioids are implicated not only for positive responses to (pleasant) music, but also for negative ones, such as, for example, sadness (Mallik et al. 2017).

In 2001, Blood and Zatorre (2001) published the first neuroimages study demonstrating that the emotional response to music was associated with increased blood flow in the brain areas associated to reward and emotion, such as the ventral striatum or the nucleus accumbens (NAcc) and the amygdala (Figure 1) (Blood and Zatorre 2001). However, these neuroimaging techniques measured the hemodynamic changes not related to specific neurotransmitters. Subsequently, Salimpoor and colleagues, using ligand-based positron emission tomography (PET), demonstrated that the musical reward specifically engages the DA system. Especially, the emotional arousal peak during music listening was associated with the release of DA in the ventral striatum or NAcc and caudate putamen (CPu) and a robust increase in connectivity between the NAcc and the auditory cortex, amygdala, and ventromedial prefrontal cortex takes place (Salimpoor et al. 2011).

In 2013, using functional MRI (fMRI), the same group found that the dorsal and ventral striatum play distinct roles. The former is activated before the maximum-pleasure moments, so it appears to be involved in mechanisms of anticipation and prediction, whereas the ventral striatum is more related to hedonic processing (Salimpoor et al. 2013). Its activity not only peaks when pleasure is maximal but also correlates with the reported degree of pleasure experienced. Additional studies confirmed these findings (Koelsch 2014; Martínez-Molina et al. 2016; Mas-Herrero et al. 2018; Müller et al. 2015).

Recent direct evidence that DA is linked to pleasure comes from Ferreri et al. (2019). In this paper, each participant received an oral administration of the DA precursor (levodopa), DA antagonist (risperidone), or placebo (lactose) and it was observed that while levodopa increased the hedonic experience and music-related motivational responses, the risperidone impaired participants' ability to experience a musical pleasure, while the placebo didn't affect the response. Thus, they demonstrated that pharmacological DA manipulation modulates affective responses to music (Ferreri et al. 2019). More recently, it has been hypothesized that DA-dependent musical reward can also improve memory not only through explicit and/or primary reinforcements, but also by musical aesthetic reward (Ferreri et al. 2021).

While many papers describe changes in DA levels as a result of the musical response, little is yet known about the chemical neurotransmitter 5-HT.

5-HT controls mood (Crispino et al. 2020) and is commonly associated with feelings of satisfaction from expected outcomes, whereas DA is associated with feelings of pleasure based on novelty or newness (Zald and Zatorre 2011). The 5-HT platelet model was found to be an appropriate model for central 5-HT neurotransmission. Indeed, platelets' 5-HT content was higher in response to pleasant music. Platelets 5-HT concentration has been assumed as a biomarker of the brain's 5-HT activity, and its decrease in depression, but these data remain disputed (Evers and Suhr 2000).

Experiments performed in rats have demonstrated that exposure to melodic music increases DA levels and the release of 5-HT in the CPu as well as DA turnover in the NAcc, suggesting that the music directly regulates monoamine activity in forebrain areas linked to reward and motor control (Moraes et al. 2018). In addition, in rats, the release of 5-HT and DA from the NAcc increased after amphetamine injection and both neurotransmitters were significantly highest in animals exposed to the music section. These findings suggest that sensorial stimuli can stimulate the same systems activated by drug use and can improve the behavioral and neurochemical responses to amphetamine administration (Feduccia and Duvauchelle 2008).

Moreover, a recent research highlighted the involvement of 5-HT 2A receptor (5-HT2AR) in changing the human perception of music following lysergic acid diethylamide (LSD) administration. In particular, Preller and Vollenweider (2018), combining neuroimaging methods and pharmacological manipulation, found that LSD administration increased the attribution of meaning to previously meaningless music and increased blood-oxygen-level-dependent signal in lateral frontal brain areas and cortical midline structures. LSD-induced effects were blocked by the selective 5-HT2AR antagonist ketanserin (Preller and Vollenweider 2018). Using another method known as tonality-tracking analysis, Barrett et al. (2018) conducted a similar study demonstrating that LSD administration changes the neural response to music in several brain regions (superior temporal gyrus, inferior frontal gyrus, medial prefrontal cortex, and amygdala); these changes are dependent on 5-HT2AR since are blocked by ketanserin (Barrett et al. 2018).

Taken together, these data increase our mechanistic understanding of the neurochemistry of music and demonstrate that pleasurable experiences, such as music listening, induce modulation of the brain monoaminergic systems.

Music therapy as adjuvant treatment for the healthy and diseased brain

Since ancient times, it has been speculated that music could have therapeutic value. This hypothesis was supported by the ancient Egyptians describing musical spells to cure the sick.

The words "music therapy" refer to the clinical approach employing music interventions, including passive/receptive listening and more active training, or performing, used to promote, maintain, and restore mental, physical, emotional, cognitive, and social individual's needs (Kennelly 2000; Pasiali and Clark 2018).

In the last 15 years clinical tests have demonstrated the music-induced benefits at cognitive, behavioral, motor, and psychosocial levels in injured, degenerating, and disordered brains (Sutcliffe et al. 2020). It has been demonstrated that music therapy can improve the expression, communication, and social interactions, and can also reduce anxiety and agitation, ameliorating the quality of life in patients suffering from various neurological disorders, including AD and PD, and ASD (Figure 2) (Guetin et al. 2009; Katagiri 2009; Sihvonen et al. 2017). Moreover, brain damages and aging greatly

Figure 2: Schematic representation of the beneficial effects of music therapy on neurological disorders.

increase the risk of developing diseases of the central nervous system, such as AD, PD, and stroke.

Below are reported some examples of music-based interventions used to slow down the physiological cognitive decline during aging, or as a therapeutic adjuvant in neurodegenerative and neurodevelopmental disorders, or after injuries (stroke).

Aging

Oxidative stress, genomic instability, epigenetic changes, mitochondrial, and lysosomal dysfunction represent the cellular basis of age-dependent deterioration and degeneration occurring in elder tissues, especially in the brain (Azam et al. 2021; Bishop et al. 2010; Mattson and Arumugam 2018). The age-related microstructural and physiological changes, at the macrostructural level are translated into cerebral atrophy with reduction of gray matter volume, especially in the hippocampus and prefrontal cortex, shrinkage of white matter connections, and expansion of cerebellar ventricles (Harada et al. 2013; James et al. 2020; Raz et al. 2005; Sowell et al. 2003). These changes reduce brain connectivity and plasticity causing a decline in attention, memory, processing speed, executive functions, cognitive flexibility, logical thinking, and auditory selective attention (Fjell and Walhovd 2010; Harada et al. 2013; Kaup et al. 2011; Salthouse 2011). Physical exercise, as well as intellectually, emotionally, and socially stimulating activities, such as listening to music or music training, delay aging and cognitive decline of elders, deferring the degeneration of the hippocampus (Baker et al. 2010; Groussard et al. 2010; James et al. 2008; Oechslin et al. 2013).

Furthermore, independent studies revealed that music training in naive old adults, not only improves mood and well-being but also enhances cognitive and sensorimotor performance, ameliorating verbal, visual, and working memory, executive functions, and auditory and verbal processing (Bugos et al. 2007; Degé and Kerkovius 2018; Guo et al. 2021; James et al. 2020; Seinfeld et al. 2013; Worschech et al. 2021). It has been demonstrated that more intense and engaging is the musical activity, more significant is the cognitive improvement (Degé and Kerkovius 2018; Guo et al. 2021). These benefits can depend on the fact that musical practice induces functional and structural plasticity in the prefrontal cortex and in the anterior and middle part of the hippocampus (James et al. 2020), delaying age-related atrophy and physiological cognitive decline. According to this hypothesis, it has been shown that the probability to develop dementia and cognitive impairments is reduced in older subjects practicing music compared to their twins (Balbag et al. 2014).

Alzheimer's disease

The most common type of dementia in the elderly is AD, an irreversible brain disorder characterized by cognitive decline, including disruptions in memory, attention, recognition, language, problem solving, and decision-making. These cognitive impairments interfere with daily life (Burns and Iliffe 2009).

In the early stages of AD, structural damages are observed in the entorhinal cortex, hippocampus, and posterior cingulate cortex (Frisoni et al. 2010), parietal lobes, orbitofrontal cortex, while the primary sensory, motor, visual, and anterior cingulate cortices are spared (Frisoni et al. 2007, 2010; Jacobsen et al. 2015; Singh et al. 2006; Thompson et al. 2003; Van Hoesen 2000; Villain et al. 2012). Despite the temporal lobes being involved in a musical memory (Peretz 1996; Samson and Peretz 2005), in AD patients' musical memory is often surprisingly well preserved (Vanstone and Cuddy 2009). AD patients are able to respond in a positive emotional manner to well recognized familiar songs, even in the late stage of the illness.

A significant number of studies have demonstrated that music therapy improves crucial functions affected in AD patients, such as attention, psychomotor speed, memory, orientation, and executive functions (Gómez-Gallego et al. 2021; Narme et al. 2013; Satoh et al. 2015). Listening to music may act as a relaxation technique, reducing behavioral agitation, evoking personal memories and associated emotions, reinforcing the sense of identity (Baird and Thompson 2018; Leggieri et al. 2019), improving verbal fluency, and mental wellbeing of patients with AD (Lyu et al. 2018). In addition, active music therapy is able to stimulate neural activity and improve cognitive functions and depression (Zhang et al. 2017b).

In conclusion, the findings described above strongly suggest that music therapy could be a promising non-pharmacological intervention improving behavior and cognition in AD. However, further investigations in this field are needed to claim the impact of music therapy on this disease.

Parkinson's disease

PD is the second most common age-related neurodegenerative disease after AD, which affects about ten million people worldwide. It is characterized mainly by a combination of motor symptoms such as resting tremor, bradykinesia, rigidity, and abnormal gait (Volpicelli et al. 2020). These deficiencies also generate several other changes, such as cognitive disorders, dysarthria, alterations in balance, and temporal and spatial perception deficits. The current treatment of the pathology is the administration of Levodopa. However, to prevent the decline of neurobiological functions such as memory and to rehabilitate gait, in addition to neurofunctional physiotherapy and deep brain stimulation, other new non-pharmacological interventions, including rhythmic auditory stimulation, have been designed (Bella et al. 2017; García-Casares et al. 2018; Pereira et al. 2019; Sihvonen et al. 2017). In recent years, several articles have analyzed the therapeutic effects of music on motor and nonmotor symptoms in PD patients, and the studies of the last 5 years were extensively summarized in a systematic review (Machado Sotomayor et al. 2021). PD patients subjected to different music therapy programs respond positively in various spheres. Some studies documented that music-based movement therapy improves the treatment of motor symptoms, and that physical activity promotes DA release and neuroprotection (Hou et al. 2017). An fMRI study demonstrated that 5 days of intensive modern dance training increased functional connectivity between the basal ganglia and premotor cortex (Batson et al. 2016). Electroencephalography studies showed changes in muscle synergy during balance and walking tests after 3 weeks of Tango classes (Allen et al. 2017; McKay et al. 2016). These results suggest that listening to music and dancing, as well as rhythmic auditory stimulation, can be useful in the maintenance of motor performance in patients affected by PD.

Other studies, through programs that focus on singing, either individually or in groups, support the use of music in the treatment of nonmotor symptoms of people with PD. These programs ameliorate the communication, swallowing, breathing, the emotional aspect, cognitive function, depressive symptoms, and overall, improve the quality of life of people with PD (Han et al. 2018). In conclusion, different music therapy programs can get better on motor and non-motor symptoms of PD patients.

Stroke

Stroke is the second most common cause of death worldwide, affecting more than 15 million people each year (Feigin et al. 2014). It is a disease of aging since most strokes occur in people over 65 years. The efficacy of music-based interventions for people affected by stroke has been often reported in the scientific literature of the last decade. Ripollés and colleagues have demonstrated that a group of individuals affected by chronic stroke showed a significant improvement in motor and cognitive functions and a reduction in depressed and negative mood symptoms after music therapy (Ripollés et al. 2016). Indeed, in these patients, mood changes and cognitive dysfunction are quite common (Nys et al. 2007). Other studies reported that listening to music after stroke promotes a structural reorganization of frontal (superior frontal gyrus) and limbic areas (anterior cingulate cortex and ventral striatum) with an increment of volume and connectivity. These changes are accompanied by a stronger recovery in motor and cognitive functions including attention, verbal memory, and language (Amengual et al. 2013; Särkämö et al. 2008, 2014; Sihvonen et al. 2021). In addition, active-music intervention, like playing musical instruments, is able to further enhance motor recovery in patients with paresis after stroke (Altenmuler and James 2020; Grau-Sánchez et al. 2020). A devastating complication of stroke is aphasia, a communication disorder, affecting the ability to write, speak and understand language. Varieties of aphasia are classified into two forms: fluent and nonfluent. Fluent aphasia is generated by a lesion involving the Wernicke's area; these patients have articulated speech, but severe speech comprehension deficits. In contrast, a lesion in Broca's area determines nonfluent aphasia; these patients have relatively intact comprehension but have marked impairments in speech production and articulation. Different rehabilitative approaches for aphasia are available; among them Melodic Intonation Therapy (MIT) is a program identified by the American Academy of Neurology as an effective form of output-focused language therapy. Patients with severe nonfluent aphasia, treated with MIT, are able to sing lyrics better than they can speak the same words (Schlaug et al. 2010). The therapeutic effect of MIT is also confirmed by neuroimaging studies that show reorganization of right-hemisphere vocal-motor network brain functions with speech output improvements (Tabei et al. 2016; Wan et al. 2014). Slavin and Fabus conducted a study of a 63-year-old man with nonfluent aphasia and apraxia of speech (altered sequence of movements involved in producing speech) using a modified version of MIT to include several vocal and linguistic tasks. At the end of the study, the participant demonstrated reduced apraxia, improvements in auditory comprehension, and expressive language skills (Slavin and Fabus 2018).

Recent results suggest that the combination of melody and rhythm makes it easier to recover speech in the treatment of aphasia (Cortese et al. 2015).

In conclusion, although it appears evident that music therapy has an excellent impact on some of the symptoms of stroke patients, more research is needed to better understand the specific contribution of the different music therapies in stroke treatment.

Autism spectrum disorders

In the last decades, particular attention has been paid to the effects of music in young people and adults with ASD, a group of heterogeneous neurodevelopmental conditions characterized by impaired social interaction and repetitive stereotyped behaviors. In addition to the core symptoms of ASD, problems related to sensory and emotional regulation, language, motor, and attentional difficulties, were found in at least 70% of patients (Tomchek and Dunn 2007). To date, ASD has no cure, and pharmacological treatments such as psychostimulants, atypical antipsychotics, antidepressants, and alpha-2 adrenergic receptor agonists, have no effects on core symptoms (Sharma et al. 2018). Several studies have reported contradictory results regarding the benefits of music therapy in children with ASD (Mayer-Benarous et al. 2021). However, current literature shows that most individuals with ASD respond positively to music, making it an excellent therapeutic tool. Music therapy can improve behavior, social interaction, verbal and gestural (nonverbal) communication (Geretsegger et al. 2014; Mayer-Benarous et al. 2021; Sharma et al. 2018). It acts to reduce negative responses, promoting self-expression, relaxation, learning, improving the quality of life and cognitive abilities, such as attention and concentration. In ASD children, music therapy also improves the relationship with parents.

In people with ASD, listening to music improves musical memory, the perception of tones, and sound frequencies. Moreover, it activates emotions and the related reward circuits (including NAcc, VTA, striatum, amygdala, prefrontal, and orbitofrontal cortex). Structural and functional changes in the brain areas that involve social communication and emotional skills were also observed (Quintin 2019; Sharma et al. 2018).

Growing evidence accentuates the importance of rhythmic auditory stimulation in improving motor skills and social, communicative potential in ASD patients (Hardy and Lagasse 2013; Srinivasan et al. 2015; Whitall et al. 2011).

Thus, the use of music as a therapeutic tool in combination with conventional therapies should be considered for ASD patients. Nonpharmacological therapies coupled with pharmacological therapies might be used as a tool to stimulate brain plasticity, improve motor control and decrease repetitive behaviors, and permit better control of the comorbid conditions expressed in ASD patients (Mayer-Benarous et al. 2021).

Conclusions

Music is an important form of communication, not uniquely human, that has played a major role in our species' brain evolution and in social aggregation.

This review summarizes the current literature on the multiple effects of music on the structural and functional rearrangement of brain circuits, emphasizing new insights of music therapy as a nonpharmacological intervention to ameliorate the physiological cognitive decline or to alleviate the core symptoms of severe illnesses such as AD, PD, ASD, and stroke.

It is now known that music changes the chemistry of the brain, affecting the DA and 5-HT release, which in turn are able to evoke emotional reactions, memories, and feelings. Several studies have analyzed the long-lasting positive effects of music therapy programs on different spheres of human behavior, showing that musical training and music-based interventions may lead to neuroplastic changes.

Listening or performing music has been reported as a way of improving quality of life, promoting self-expression, relaxation, learning, and reducing negative responses. Therefore, music represents an effective method to improve social interaction and well-being in the elderly or in patients with neurodegenerative or neurodevelopmental disorders, such as AD, PD, and ASD. Music therapy programs based on listening, body rhythm, and rhythmic auditory stimulation exert positive effects also on motor symptoms of many brain dysfunctions.

For this reason, future investigations should better evaluate the potential benefits of music and the different mechanisms of action required, with a particular interest in music as a powerful tool to improve wellness in several illnesses.

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